REMARKS

By this amendment, claims 71, 91, 98-99, and 101 have been amended. New claim 112 has been added. Support for the amendments is found in the specification on pages 13 and 15, in the Tables, and in the original claims as filed.

I. Objections

The Examiner indicates that claims 57-70, 72-85, 90, and 104-108 would be allowable except for depending from a rejected base claim (claim 56). The Examiner suggested re-writing these claims in independent form.

Instead, Applicants respectfully traverse the rejection of claim 56, for reasons presented in section III, below. It is respectfully requested that if the Examiner reconsiders his rejection of claim 56 and finds that claim allowable, then dependent claims 57-70, 72-85, 90, and 104-108 also be allowed.

II. Claim Rejections Under 35 U.S.C. §112-Indefiniteness

Claim 71 stands rejected for depending on a canceled base claim (claim 12). By this amendment, claim 71 has been amended to depend from a pending claim, thereby obviating the rejection.

Claim 91 stands rejected as indefinite for reciting both a broad range and a narrower, preferred limitation within the broad range. To overcome this rejection, claim 91 has been amended to recite only the broad range, and new claim 112 has been added which recites the narrower limitation. Accordingly, withdrawal of this rejection is requested.

III. Claim Rejections Under 35 U.S.C. §103-Obviousness

Claims 51, 55, 56, 86-89, 91-99, 101-103, and 109-110 have been rejected as being obvious over Roser et al. (U.S. Patent No. 5,958,455; filed 2/9/96 and issued 9/28/99). The Examiner contends that Roser teaches a process of making an effervescent progesterone tablet

which includes the preparation steps set forth in the rejected claims, and that Roser teaches a tablet comprising micronized progesterone.

The Examiner acknowledges that Roser does not teach or suggest using microgenized progesterone, or the precise ordering of steps called for in the instant claims, however he contends that it would have been obvious to one of ordinary skill in the art to produce the tablet according to the method instant claims. The Examiner asserts that Roser provides both the suggestion and the motivation. Using this reasoning, the Examiner further incorrectly asserts that the oral tablet produced by the distinct method Roser also renders the claimed vaginal tablet obvious.

Applicants respectfully traverse this rejection. First, if the Examiner acknowledges that Roser does not teach or suggest the use of micronized progesterone, or the precise ordering of steps recited in the instant claims, Roser cannot render the present claims obvious. To meet the burden of *prima facie* obviousness under 35 U.S.C. §103(a), the Examiner must establish that three criteria have been met. First, there must be a concrete suggestion or motivation to modify what is taught in a reference or to combine its teachings with other references. Second, there must have been a reasonable expectation that the modifications or combination would succeed. Finally, the combined or modified prior art must actually teach all of the claimed limitations. Both the motivation and the reasonable expectation of success must be found in the prior art and not in Applicants' disclosure. See, M.P.E.P §2143; citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The present claims are not obvious because one of ordinary skill in the art would not have been motivated to modify the Roser teachings to arrive at the invention defined by the present claims. This is detailed further below.

Regarding the method of use claims 55, 56, 86-89, 91-97, and 109-110, although Roser teaches a number of ways to make an oral effervescent progesterone tablet, he does not teach or suggest the steps of the present claims, which are directed, in part, to a method of making a vaginally-administrable effervescent tablet. What Roser teaches is a method of dry direct

compression that involves using the sugar, trehalose, as an tabletting excipient. Roser specifically discloses that the tablets can be produced from various physical forms of powdered, trehalose, including crystalline trehalose, vitreous (i.e., glass-like) trehalose, and anhydrous trehalose containing less than 2% water. Roser further teaches that his method "can be used to produce tablets of even higher quality than lactose tablets without....combining all the components in aqueous solution prior to powder formation" (see column 5, lines 11-16).

While Roser does teach in one embodiment that the active agent can be incorporated in to a solution of trehalose (*i.e.*, a mixture of trehalose and the active ingredient), and dried to form a trehalose matrix, prior to blending with other ingredients and tabletting (column 5, l ines 45-49), Roser does not teach or suggest pre-wetting and drying only the active-ingredient, prior to mixing with other ingredients and tabletting by dry direct compression. This embodiment is claimed in independent claim, claim 1. In another embodiment, Roser teaches combining all of the tabletting components in solution or suspension in an aqueous solvent, and then processing the solution to form a powder, prior to tabletting (see column 7, line 61, to column 8, line 9). Again, this is clearly distinct from the present claims, which are directed to a method of first pre-wetting and drying only the active ingredient (i.e., micronized progesterone). In a third embodiment, Roser teaches combining effective amounts of trehalose, active agent and excipients in powder form, mixing the ingredients until homogenous, and tabletting (see column 8, lines 30-37). This third embodiment is claimed in claim 11. Nowhere does Roser disclose or suggest pre-wetting and drying only the active ingredient prior to the addition of any other ingredients, as called for in the present claims.

Even assuming, *arguendo*, that one of ordinary skill in the art would be motivated to make a vaginally administrable, effervescent tablet (containing, of course, anhydrous trehalose) from the teachings of Roser, there could be no reasonable expectation of success since there is no teaching in Roser that trehalose can be metabolized by the vagina, much less dissolved completely in 6-10 hours as called for in the present claims to the tablet (as amended herein). Column 4 discloses that trehalose is metabolized by the enzyme *trehalase*, which is found on the membrane of the intestinal tract. Column 4 also discloses parenteral administration of trehalose

is beneficial precisely because it cannot be metabolized (to glucose) in the bloodstream (thereby avoiding elevating blood glucose). Since the unexpected superior property of the effervescent tablet of the present invention is that it dissolves rapidly and completely in the vagina, without leaving any particulate residue behind (see inventor Declaration submitted July 15, 2002), one of ordinary skill in the art would not be motivated to include an ingredient, *i.e.*, trehalose, which cannot be metabolized in the vagina. Accordingly, withdrawal of the obviousness rejection is respectfully requested.

In view of the foregoing, it is clear that the teachings of Roser do not render the present claims obvious according to the aforementioned criteria. There is no concrete suggestion or motivation in Roser, or in the relevant field, to modify the method of Roser by pre-wetting and drying only the active-ingredient and drying it prior to mixing it with any other tabletting ingredients. Since Roser does not disclose or suggest the foregoing, it is therefore not possible that one of ordinary skill in the art, reading Roser, would have had a reasonable expectation that such an undisclosed modification would succeed (i.e., would disintegrate rapidly in the vagina). It is also impossible for Roser to meet the third criteria, i.e., to teach all of the claimed limitations, since Roser does not teach or suggest pre-wetting and drying only the active-ingredient and drying it prior to mixing it with any other tabletting ingredients, and further does not teach that trehalose, the critical feature of his invention, can be used in a vaginally administrable formulation. Applicants assert that the Examiner is incorrectly relying on the disclosure of the present application to supply the missing teachings and motivation.

Accordingly, withdrawal of the rejection of claims 55, 56, 86-89, 91-97, and 109-110 is respectfully requested.

Regarding the Examiner's assertion that the tablet disclosed in Roser renders the presently claimed tablet obvious (claims 51, 98-99, and 101-103), Applicants have amended claims 98-99 and 101 by this amendment. Support for this amendment is found in the specification in the Tables on pages 12 and 15. In view of this amendment, Applicants emphatically assert that Roser does not disclose or suggest tablets for vaginal administration,

which contain micronized progesterone in combination with a non-effervescent excipient or diluent, and an effervescent, as presently claimed. As indicated by the title of the Roser patent, Roser's tablets, produced by his claimed method, are for oral delivery. At column 2, lines 1-20, in the Background section, Roser discloses other compressed tablets for non-oral delivery that are produced by compression, including vaginal suppositories such as Metronidazole Tablets, which contain lactose as the diluent. (Metronidazole is used to treat a variety of bacterial and parasitic infections, such as amebiasis, trichomoniasis, and giardiasis). Also within that paragraph, Roser discloses that some compressed tablets can be effervescent. However, this statement is not in reference to the vaginal suppositories, and does not teach or suggest that the vaginal suppositories can be effervescent. Further, Roser discloses a progesterone tablet only in the context of buccal or sublingual administration (column 2, line 21-22), or in the context of his own, trehalose-containing oral tablet (column 11, line 64). Roser does not disclose micronized progesterone.

Accordingly, there is certainly no suggestion or motivation in Roser that would lead those skilled in the art to modify his oral tablet (containing trehalose), to make it suitable for vaginal administration, and specifically contain micronized progesterone as the active ingredient, *much less* make the tablet effervescent, thereby effecting dissolution in the vagina within 6-10 hours. Moreover, one of ordinary skill in the art, or even one of no skill in the art, would not be motivated to make a vaginal effervescent tablet from the disclosure of Roser's oral tablet in view of the discussion above regarding the metabolism, or non-metabolism, of trehalose in the vagina.

Inventor Declaration

Lastly, Applicants would like to re-emphasize the unexpected, superior properties of the presently claimed tablet, as described in the Inventor Declaration filed on July 15, 2002, and in the subsequent Response filed February 18, 2003. The unexpected clinical benefit of the presently claimed tablet and method of producing such tablet lies in the enhanced dissolution

properties when the pre-wetted and dried micronized progesterone is combined with an effervescent.

It is therefore respectfully requested that this evidence be properly considered by the Examiner, pursuant to MPEP Section 2144.08 (B). According to the MPEP, "rebuttal evidence" that can be used to overcome a *prima facie* case of obviousness includes evidence of secondary considerations, such as the resolution of a long-felt, but unsolved need, commercial success, and the possession of unexpectedly improved properties. The above-referenced discussion, and inventor declaration, provides concrete evidence to support all the aforementioned secondary considerations. The tablet unexpectedly dissolves rapidly and leaves no residue, overcoming the patient discomfort caused by the prior art tablets, thereby satisfying the first and third considerations. In addition, the inventor declaration indicates that these tablets have been approved by the Israel Ministry of Health and are commercially available in Israel under the name Endometrin®.

In view of the foregoing evidence, it is respectfully requested that the claims be allowed and the cased be passed to issue.

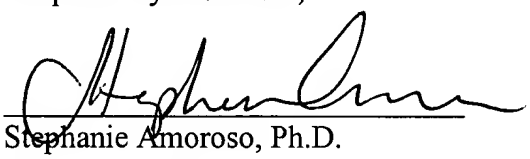
Applicants contend that neither the pre-wetting of the mirconized progesterone, nor the surprising benefit conferred

CONCLUSION

Applicant respectfully requests entry of the foregoing amendments and remarks. All of the alleged grounds for unpatentability of the claims have been addressed by this response. Applicant earnestly solicits allowance of the application.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,



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